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09/210,747	12/15/1998	ROBERT E BRIGGS	0029577957	4952

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EXAMINER
PORTNER, VIRGINIA ALLEN

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/210,747	Applicant(s) Briggs et al
	Examiner Portner	Art Unit 1645

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 8, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *40-44, 46-49, and 51-62* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *40-44* is/are allowed.

6) ☒ Claim(s) *46-49 and 51-62* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 34-35,38-39, 45 and 50 have been canceled.

Claims 40-44,46-49, 51-62 are pending.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Allowable Subject Matter

2. Claims 40-44, upon processing the terminal disclaimer submitted April 7, 2000 and it being found proper define over the prior art of record.

Rejections Maintained

3. Claims 46-49, 51-62 rejected under 35 U.S.C. 112, first paragraph (scope of enablement for vaccine compositions), because the specification, does not provide enablement for Pasteurella haemolytica vaccines that comprise any mutations in the leukotoxin C, A, B or D genes and the use of these strains as a vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the claimed inventions, and to use them as vaccines for reasons of record in paper number 16, as applied to claims 46-47, paragraph 9 and for reasons of record in paper number 19, paragraphs 9-13.

4. Claims 46-49 and 51-62 (new claims) rejected under 35 U.S.C. 112, first paragraph *(written description)*, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had *possession* of the claimed invention, for the same reasons as

applied to claims 48-49, made of in paper number 16, paragraph 10; and for reasons of record in paper number 19, paragraphs 9-13.

Response to Arguments

5. The rejection of claims 46-49, 51-62 under 35 U.S.C. 112, first paragraph, because the specification, does not provide enablement for Pasteurella haemolytica vaccines that comprise any mutations in the leukotoxin C, A, B or D genes and the use of these strains as a vaccine is traversed on the grounds (Applicant's response, page 2, paragraph 2):

a. "the specification need not provide knowledge that is generally known in the art"; and

b. "all that is required to enable a genus claim is that there is a reasonable correlation between the disclosure and the scope of the claim."

6. In response to the above arguments, the examiner would like to quote a different portions of Applicant's response at page 9, first full paragraph "None of the vaccines disclosed in these publications is taught to comprise an attenuating mutation in a leukotoxin A,B,C or D gene."

Clearly in view of the cited vaccine art provided in Applicant's response dated November 8, 2002 (pages 8-9) leukotoxin mutant Pasteurella haemolytica vaccines are not generally known in the art. The specification does not provide any added knowledge and the knowledge that is generally known in the art does not define any Pasteurella haemolytica vaccines with mutations in a leukotoxin gene (A, B, C or D open reading frames) .

Chidambaram et al (1995) shows the production of phenotypically leukotoxin negative strains of Pasteurella, and teaches "[S]ince no mutagenesis procedure had been published previously for P.haemolytica, it was first necessary to establish a mutagenesis protocol. (See page 1028, col. 2, paragraph 4)" Problems existed in the art of Pasteurella haemolytic mutagenesis because this bacterium carries a prophage that is induced by many DNA-damaging treatments (Richards et al, Am. J. Vet. Res., Vol.46, pages 1215-1220, 1985). Thus, any mutagen that was used should avoid prophage induction." Production of mutant strains of Pasteurella haemolytica is taught to be complicated and thus unpredictable due to the presence of a prophage induced by treatment of P.haemolytica DNA with a mutagen. The instant specification does not teach any specific method or protocol to prevent the induction of P.haemolytica's prophage; prophage activation would preclude the production of a living mutant strain of P.haemolytica. Chidambaram et al also teach that "genetic mapping is not yet possible for P.haemolytica (see page 1030, col. 1, paragraph 3).

The claimed invention is directed to any type mutant strain, as long as some degree of over all attenuation of the cell is accomplished. The leukotoxin expressed by the mutant Pasteurella must result in an attenuated mutant, but the leukotoxin is not required to be deleted, or completely inactivated; the mutation must only result in some degree of attenuation.

Whole cell Pasteurella vaccines are discussed by Potter: (see col. 2, lines 2-10, Potter, US Pat. 5,871,750) "[T]raditional vaccine preparations, however, have not been effective in protecting against Pasteurella infections. Indeed, vaccinated animals are frequently more

susceptible to the disease than their non-vaccinated counterparts. (Martin et al (1980) Can. J. Comp. Med. 44:1-10. The lack of protection offered by traditional vaccines is probably due to the absence of important antigen, virulence determinants, or the presence of immunosuppressive components in the preparations. Weekley et al (July 1993) utilized attenuated strains (avirulent strains, see page 90, col. 2, paragraph 4) and supports Potter's position, in teaching "vaccination with live strains of P.haemolytica cause subclinical disturbances in the pulmonary circulation and may potentially alter the animals' response to pathogens (abstract)." Kiorpes et al (1991) adds their support to this position, by teaching "vaccination of lambs with a modified-live Pasteurella haemolytica vaccines does not appear to be an efficacious preventive strategy for ovine enzootic pneumonia. (See Kiorpes et al, see abstract and page 81, paragraph 4)" .

Summit et al (1990, Biotechnology news) shows a leukotoxin containing vaccine that produced inconsistent results, wherein under controlled conditions the vaccine appeared to work, while under field trial conditions all vaccinated and control animal "got ill within a few days of vaccination", while in a second trial none of the animals got sick, including the control animals." The instantly claimed mutant strains are not leukotoxin negative, but must only comprise a mutation that attenuates the activity of the encoded leukotoxin.

Gentry et al (April 1988, abstract) teaches that various serotypes produce leukotoxin with varied total toxic activity, as well as varied in leukotoxin production. A strain of P.haemolytica that produces a less toxic form, and differs in the kinetics of leukotoxin production,

would be a naturally occurring mutant strain that is attenuated relative to other virulent strains of Pasteurella.

The instantly claimed genus claims directed to Pasteurella haemolytica mutant bacterium with a mutation in a leukotoxin A gene, leukotoxin B gene, leukotoxin D gene or leukotoxin C gene, does not evidence a "reasonable correlation between the disclosure and the scope of the claim" because no guidance, direction, sequences, or showing of induction of a Protective immune response with a leukotoxin gene mutant has been disclosed, and this type of vaccine is Not generally known in the prior art . The instant specification provides only a probable suggestion. Arguments set forth in paper number 19, paragraphs 9-13 are incorporated herein by reference.

7. Applicant asserts that the "Office Action dismisses the Declaration", asserts that there is no legal basis for ignoring the Declaration, and the vaccine of the mutant bacterium with a mutation in a leukotoxin gene works exactly as the specification teaches.

8. It is the position of the examiner that the Declaration was considered (see pages 4-5, paper number 19), the Declaration was not ignored.

The Declaration discusses and provides data for a specific mutation. The specification does not teach a mutation of the coding sequence for amino acids 34-378 of the open reading from for leukotoxin A using the strain of Pasteurella haemolytica used to produce the submitted data. Where in the specification the specific mutation discussed in the Declaration is taught was not pointed out. The Declaration provides data that is directed to a deletion mutant, of a

specific size, in a specific location of the coding sequence; all of these features are not disclosed or described or even suggested. The specification does not provide original descriptive support for the specific embodiment used to generate data provided in the Declaration. Lack of written description to provide enablement has a legal basis in 35 U.S.C. 112, first paragraph. The rejection of the claims was set forth under this statute.

The phrase (Instant specification, page 7, lines 11-12) "Other genes in which mutations *may be desirable* are genes in the leukotoxin operon (C,A,B,D)" does not define the bacterial mutants to "work exactly" like a vaccine. Leukotoxin phenotypes are not discussed in the instant specification. No specific functions are set forth for the leukotoxin mutants.

Davies et al (Journal of Bacteriology, Vol. 183 and Vol. 184) teach that the leukotoxin operon evidences many structural allelic variations (see Vol. 183, pages 1394-1403), is highly polymorphic with multiple alleles (see Vol. 184, page 267, col. 1, paragraph 2).

Davies et al (Vol. 183, page 1396, Table 1) shows that there are at least 14 different coding sequences for leukotoxin A, with variations in nucleotide and amino acid sequence from 1.0 to 17 % (see Vol. 183, page 1397, Table 2 and page 1399, Figure 3).

Davies et al (Vol. 184, page 269, col. 2, paragraph 3) teaches that there are 12 different leukotoxin C coding sequences (see Vol. 183, figure 2, page 270), 19 different leukotoxin B sequences (see Vol. 183, figure 3, page 270) and 11 different leukotoxin D sequences (see Vol. 183, figure 4, page 271). None of these gene sequences have been described in the instant specification and they were not generally known in the art at the time of filing of the instant specification.

9. Applicant asserts that [T]he specification teaches how to make mutations in the four genes", as "well as how to prepare and administer the claimed vaccines".

10. It is the position of the examiner that absence specific guidance, any general method of chemical treatment of a P.haemolytica strain would not result in a viable, leukotoxin mutant strain that would function as a vaccine strain. Chidambaram et al (1995) teaches general chemical treatment of P.haemolytica strains does not result in a viable mutant strain. Chidambram et al teaches that as of 1995 a published method for the production of leukotoxin mutants was not known in the art. Chidambram et al teaches: "[S]ince no mutagenesis procedure had been published previously for P.haemolytica, it was first necessary to establish a mutagenesis protocol. One complication was the fact that this bacterium carries a prophage that is induced by many DNA-damaging treatments (Richards et al, Am. J. Vet. Res., Vol.46, pages 1215-1220, 1985). Thus, any mutagen that was used should avoid prophage induction."

11. Applicant at page 11, paragraph 1, asserts that "Any experimentation required for one of skill in the field of the invention to make and use the claimed vaccines would at most involve routine procedures.

12. It is the position of the examiner, based at least upon the published article of Chidambaram et al (1995), general chemical mutagenesis of P.haemolytica to produce a leukotoxin mutant does not "involve routine procedures", but development of a mutagenesis protocol was required prior to attainment of the leukotoxin mutants. Problems associated with chemical mutagenesis of

P.haemolytica result from a carried prophage which is induced by DNA-damaging chemical treatments; prophage induction precluding the production of a viable leukotoxin mutant strain.

13. The rejection of claims 46-49 and 51-62 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is argued by asserting that:

a."[T]he specification explicitly describes the use of P.haemolytica bacteria with mutations in these genes as vaccines(instant specification page 7, lines 11-12)" and page 8, lines 28-31 and page 9, lines 1-5.

14. It is the position of the examiner that the sentence at page 7 of the instant specification sets forth two protein virulence factors for P.haemolytica, specifically leukotoxin and neuraminidase.

The coding sequence for neuraminidase was not known at the time of filing of the instant specification and the sequence was not disclosed therein, thus the phrase at page 7 with respect to neuraminidase was clearly prophetic to specific mutations in the coding sequence for the protein.

Additionally, leukotoxin mutants are mentioned at the same location, page 7, but no specific strain or strains were described to evidence a non-reverting mutation, that is a deletion or insertion mutation.

The narrative quoted at page 8, lines 28-31 and page 9, lines 1-5, is descriptive narrative with respect to mutant strains produced by "site-directed mutagenesis" (see page 8, lines 24-31).

No specific sites for mutagenesis are disclosed, discussed and suggested for any specific strains of P.haemolytica. Davies et al (Journal of Bacteriology, Vol. 183 and Vol. 184) teach that the leukotoxin operon evidences many structural allelic variations (see Vol. 183, pages 1394-1403), is highly polymorphic with multiple alleles (see Vol. 184, page 267, col. 1, paragraph 2) which encode differing amino acid sequences, and the sites of variability is not limited to any one specific region of the coding sequences for each open reading for leukotoxin A, C, B or D proteins.

Therefore narrative set forth in the specification directed to site directed mutagenesis, for a coding sequence not described, in locations not suggested or taught, for any one leukotoxin coding sequence obtained from any strain or serotype of P.haemolytica does not define subject matter described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

15. The leukotoxin genes are asserted to be well known in the art.

16. It is the position of the examiner that Davies et al made public in 2001-2002 (Journal of Bacteriology, Vol. 183 and 184) that the leukotoxin operon evidences many structural allelic variations (see Vol. 183, pages 1394-1403) which are highly polymorphic (see Vol. 184, page 267, col. 1, paragraph 2) . The highly pleomorphic nature of leukotoxin genes due to many allelic variations was not well known at the time of filing, and the claims are not limited to the sequence,

species or strain for which the sequences were known and there is no guidance to utilize any specific sequence or strain (s) in the production of claim mutants.

The coding sequences for the various capsular serotypes of P.haemolytica were not well known in the art at the time of filing.

17. The Highlander reference is asserted by Applicant as having "no relevance for whether the present specification sufficiently describes the subject matter of claims 46-49 and 51-62.

18. It is the position of the examiner that the instant specification does not describe the instantly claimed genus of mutant vaccine strains of P.haemolytica which evidence any level of attenuation, produced by any method, in light of arguments set forth above by the examiner, showing evidence of highly pleomorphic alleles existing within the leukotoxin operon (Davies et al, 2001 and 2002 references) and that many different coding sequences exist for P.haemolytica leukotoxin genes. Additionally, Chidambaram et al (1995) was cited for teaching that without a specific chemical mutagenesis protocol which avoids induction of a carried prophage present in P.haemolytica DNA, induction of Pasteurella's prophage precludes successful attain of a viable mutant strain of P.haemolytica.

The Highlander et al reference was addressed by the examiner in light of Applicants discussion of the reference in paper number 17, page 12, submitted February 13, 2001, relative to the instantly claimed invention. It is true the examiner acknowledged the coding sequences of the Highlander et al strain were known, but the instantly claimed invention is directed to vaccine

compositions of mutants; no vaccines strains of P.haemolytica mutants are disclosed in Highlander.

19. At page 13, paragraph 3 of the Amendment submitted November 8, 2002, it is asserted that "[N]one of the claims recites a specific mutant strain. Thus, description of such strains is not required to demonstrate that Applicants possessed the claimed generic invention."

20. It is the position of the examiner that Applicant's Declaration set forth data for a species of mutant strain of P.haemolytica, which was not specifically suggested or taught, the data in the Declaration being asserted as showing enablement for the generically claimed vaccines of leukotoxin mutant strains of Pasteurella haemolytica.

As previously made of record, the position of the examiner is that no leukotoxin A, B, C or D mutant strains of Pasteurella haemolytica that would serve to induce a protective immune response have been described in the instant specification. The instantly claimed invention is directed to any and all mutant strains of Pasteurella haemolytica, but the subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai

Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483.

Claim Rejections - 35 U.S.C. § 102

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. Claims 47, 55-56 are rejected under 35 U.S.C. 102(b) as being anticipated by Ricketts et al (Third International Veterinary Immunology Symposium Budapest, Hungary, August 17-20 1992, abstract PS7.19).

Ricketts et al disclose the instantly claimed invention directed to a Pasteurella haemolytica mutant strain with a mutation in leukotoxin A. The encoded toxin was not expressed, and now protein visualized in immunoanalysis. The whole cell Pasteurella haemolytica leukotoxin mutant strain was administered in vivo to goats and cattle, and showed reduced incidence of lung lesions as compared to a wild type strain. The mutant strain was formulated and administered to goats and cattle (second to last line of abstract).

Inherently the Pasteurella haemolytic leukotoxin mutants of Ricketts et al (1992) anticipate the instantly claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states "Artisans of ordinary skill may not recognize the inherent characteristics or

functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. "The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

23. Claims 46-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Chidambaram et al (May 1992, B-143) as evidenced by Chidambaram et al (1995, Infection and Immunity).

Chidambaram et al (1992) disclose the instantly claimed invention directed to Pasteurella haemolytica mutants in the leukotoxin genes. The reference discloses two mutant strains (see abstract B-143, line 2) that were negative for leukotoxin production (see abstract, line 3). Chidambaram et al (1995) provides evidence that the leukotoxin mutant strains were the result of mutations effecting the leukotoxin A gene (no protein expressed, see Figure 3, page 1030), as well as effected the overall genomic arrangement of the leukotoxin operon (see page 1030, col. 2, mutant 59B0072), which introduced mutations into leukotoxin genes C, D and B.

Inherently the Pasteurella haemolytic leukotoxin mutants of Chidambaram et al (1992) anticipate the instantly claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render

the old composition patentably new to the discoverer. "The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

Conclusion

24. This is a non-final action.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

vgp
February 27, 2003

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